

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problems Mailbox.**

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11)

Publication number:

**0 396 404
A1**

(12)

EUROPEAN PATENT APPLICATION

(21)

Application number: 90304792.6

(51)

Int. Cl.⁵: **A61K 31/445, A61K 31/19,
A61K 31/135, A61K 9/24**

(22)

Date of filing: 02.05.90

(30)

Priority: 03.05.89 US 346687

(43)

Date of publication of application:
07.11.90 Bulletin 90/45

(84)

Designated Contracting States:
GR

(71)

Applicant: **SCHERING CORPORATION**
2000 Galloping Hill Road
Kenilworth New Jersey 07033(US)

(72)

Inventor: **Cho, Wing-Kee P.**
R.D. 4, 12 Dana Court
Princeton, New Jersey 08540(US)
Inventor: **Vadino, Winston A.**
9 Glenmont Road
Whitehouse Station, New Jersey 08889(US)
Inventor: **Chaundry, Imtiaz A.**
18 Rose Avenue
North Caldwell, New Jersey 07006(US)

(74)

Representative: **Ritter, Stephen David et al**
Mathys & Squire 10 Fleet Street
London EC4Y 1AY(GB)

(54)

Pharmaceutical composition comprising loratadine, ibuprofen and pseudoephedrine.

(57)

Pharmaceutical compositions for use in the treatment of cough/cold symptoms comprising loratadine, ibuprofen and pseudoephedrine are disclosed.

EP 0 396 404 A1

PHARMACEUTICAL COMPOSITION COMPRISING LORATADINE, IBUPROFEN AND PSEUDOEPHEDRINE

BACKGROUND OF THE INVENTION

The present invention relates generally to novel pharmaceutical compositions of matter comprising the non-sedating antihistamine loratadine or the decarbalkoxylation product thereof (i.e. 6-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]-pyridine), in combination with the non-steroidal anti-inflammatory drug ibuprofen, the decongestant pseudoephedrine, and suitable pharmaceutically acceptable non-toxic carriers or excipients, and to methods of using said compositions in the treatment, management or mitigation of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith.

Non-narcotic analgesics, most of which are also known as non-steroidal anti-inflammatory drugs, such as ibuprofen, are widely administered orally in the treatment of mild to severe pain, and have been disclosed as useful in treating cough/cold symptoms in combination with certain antihistamines and decongestants. See, for example U.S. Patents 4,552,899, 4,619,934 and 4,783,465, all to Sunshine et al.

SUMMARY OF THE INVENTION

It is a primary object of the present invention to provide a novel sustained release pharmaceutical composition of matter comprising a combination of an analgesically effective amount of ibuprofen, an antihistaminic-effective amount of loratadine and a decongestant-effective amount of pseudoephedrine in a pharmaceutically acceptable carrier.

It is a further object of the present invention to provide methods for the symptomatic relief of cough, cold, cold-like and flu symptoms by the administration of preselected dosages of the pharmaceutical compositions of the present invention. Cold-like symptoms as used herein refers to coryza, nasal congestion, upper respiratory infections, allergic rhinitis, otitis, sinusitis, etc.

DETAILED DESCRIPTION OF THE INVENTION

A combination dosage form especially suitable for administration of a combination comprising ibuprofen, loratadine or its decarbalkoxylation product, and pseudoephedrine or a pharmaceutically acceptable salt thereof is disclosed. The dosage form provides for the sustained release of ibuprofen and pseudoephedrine or a salt thereof, preferably the sulfate, and the immediate release of loratadine or its decarbalkoxylation product, since the latter are inherently long-acting. Release of ibuprofen and pseudoephedrine takes place over 2 to 16 hours, preferably 5 to 12 hours. One or two, preferably two tablets are administered at a time. Concentration ranges for the actives are as follows: pseudoephedrine salt, 30-240 mg/tablet; ibuprofen, 100-800 mg/tablet; and loratadine or its decarbalkoxylation product, 0.5-10 mg/tablet. The concentration ranges represent about 3 to about 25% of coated tablet weight for pseudoephedrine salt, about 10 to about 55% for ibuprofen, and about 0.05 to about 1.5% for loratadine.

The preferred dosage form is a coated tablet, wherein loratadine or its decarbalkoxylation product is present in the tablet coating and ibuprofen and the pseudoephedrine salt are present in the tablet core, which core also comprises a swellable hydrophilic polymer as a binder. When the dosage form comes into contact with gastric or aqueous media, the coating dissolves rapidly to release loratadine and the core hydrates and slowly releases ibuprofen and pseudoephedrine by erosion of the hydrated layer and/or by diffusion of drug through the core. The rate and duration of release is controlled by the relative concentration of the hydrophilic polymer, as well as by the particular characteristics of the hydrophilic polymer selected.

Loratadine, the USAN chemical name of which is ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-carboxylate, is claimed in US Patent 4,282,233, and its decarbalkoxylation product, 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]-pyridine, claimed in US Patent 4,659,716. Pharmaceutically acceptable salts of loratadine and its decarbalkoxylation product are also contemplated for use in the present invention. The dosage range for both

loratadine and its decarboxylation product is about 0.5 to about 10 mg per day, preferably about 5 to about 10 mg/day, depending on the age, weight, condition, etc. of the patient.

Typical swellable hydrophilic polymers include cellulosic ethers such as methylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, hydroxy-ethylcellulose, carboxymethylcellulose and carboxyethylcellulose, or mixtures thereof, with hydroxypropylmethylcellulose (HPMC) being preferred. Particularly useful HPMC polymers are HPMC USP 2910 and USP 2208, for example The Dow Chemical Company's METHOCEL E4M, E15M and K100M, wherein the designation "E" refers to USP 2910 and the designation "K" refers to USP 2208, and wherein the number designation refers to the viscosity in a 2% aqueous solution (e.g. 4M designates a viscosity of 4000 cps) and indicates the number average molecular weight (Mn) of the polymers (E4M has Mn 86,000, E15M has Mn 120,000, and K100M has Mn 246,000). The hydrophilic polymer or polymer mixture is present at a concentration of about 5 to about 15% of the tablet core weight.

The tablet core optionally further comprises excipients such as insoluble polymers, soluble or insoluble fillers, antiadherents, lubricants and additional binders. Typical fillers include dibasic calcium phosphate and the dihydrate thereof, microcrystalline cellulose and lactose, with microcrystalline cellulose being preferred. Fillers are present at a concentration of about 10% to about 20% of the tablet core weight. Antiadherents, used to prevent tablets from sticking to the tablet press, typically include silicas such as silicon dioxide and talc, and are present at a concentration of 0 to about 5% of the tablet core weight. Typical lubricants are magnesium stearate and stearic acid, present at a concentration of about 0.25 to about 5% of the tablet core weight. Additional binders used in the granulation of the drug-polymer mixture typically include povidone and cornstarch. Such binders are present at a concentration of about 0.5 to about 3% of the tablet core weight.

The tablet coating comprises, in addition to the active, a hydrophilic polymer as described above, preferably HPMC, and a plasticizer such as polyethylene glycol (PEG). A preferred HPMC for tablet coating is HPMC 2910 having a viscosity of 4-60 cps in a 2% aqueous solution, more preferably having a viscosity of 6 cps. The PEG preferably has a molecular weight of 300-6000. The ratio of polymer to plasticizer is about 2:1 to about 5:1, with 5:1 being preferred.

For preferred compositions of the present invention, either the ibuprofen or the pseudoephedrine (or salt thereof) is also coated with HPMC-PEG as described for the tablet coating in order to avoid stability problems arising from the physical incompatibility of ibuprofen and pseudoephedrine.

The methods of preparing compositions of the present invention, e.g. granulation, tablet compression and tablet coating, are all well known to those skilled in the art.

EXAMPLE 1	
A. Core Tablet	
	mg/tablet
Pseudoephedrine Sulfate	120
Ibuprofen 90%*	555
HPMC K100M	100
Povidone	10
Microcrystalline Cellulose	154
HPMC/PEG	28
Magnesium Stearate	5
	<u>972</u>
*Equivalent to 500 mg ibuprofen	
B. Active Coating	
Loratadine	5
HPMC/PEG	10

Method of Manufacture

A. Core

1. Blend pseudoephedrine sulfate, microcrystalline cellulose and HPMC K100M for 5-30 minutes in a suitable mixer.
- 5 2. Dissolve povidone in a hydroalcoholic mixture and use it to granulate the powder mix.
3. Dry and mill the pseudoephedrine sulfate granulation using suitable size screen.
4. Coat ibuprofen with HPMC/PEG solution in a suitable coater (see part B below).
5. Blend the screened pseudoephedrine sulfate granulation with coated ibuprofen and remaining ingredients for 3-15 minutes.
- 10 6. Compress into suitable size tablets.

B. Ibuprofen coating

1. Dissolve HPMC and PEG in suitable amount of water.
- 15 2. Coat ibuprofen with the HPMC/PEG solution in a suitable coater.

C. Active Loratadine Coating

1. Dissolve HPMC/PEG in suitable amount of water or a water/alcohol mixture.
- 20 2. Disperse loratadine in the HPMC/PEG solution.
3. Coat tablets with the dispersion and polish the coated tablets using standard procedures.

EXAMPLE 2	
A. Core	
	mg/tablet
Pseudoephedrine Sulfate	120
Ibuprofen 90%*	555
HPMC E4M	150
Povidone	7.5
Microcrystalline Cellulose	148.5
Silicon Dioxide	14
Magnesium Stearate	5
	<u>1000</u>

* Equivalent to 500 mg ibuprofen

B. Coating

Loratadine	5
HPMC/PEG	10

Method of ManufactureA. Core

- 50 1. Blend pseudoephedrine sulfate, microcrystalline cellulose and HPMC E4M for 5-30 minutes in a suitable mixer.
2. Dissolve povidone in a hydroalcoholic mixture and use it to granulate the powder blend.
3. Dry and mill the pseudoephedrine sulfate granulation using suitable size screen.
4. Blend the pseudoephedrine sulfate granulation, ibuprofen and remaining ingredients for 3-15 minutes.
- 55 5. Compress into suitable size tablets.

B. Active Loratadine Coating

1. Dissolve HPMC and PEG in suitable amount of water.
2. Disperse loratadine in the HPMC/PEG solution.
3. Coat tablets with the dispersion and polish the coated tablets using standard procedures.

A similar dosage form comprising the non-steroidal anti-inflammatory drug acetaminophen in place of ibuprofen is also a part of the present invention. The dosage form releases acetaminophen and pseudoephedrine over 2 to 16 hours, preferably 5 to 12 hours, and immediately releases loratadine. Concentration ranges for the actives are as follows: pseudoephedrine salt, 30-240 mg/tablet; acetaminophen, 100-500 mg/tablet; and loratadine or its decarbalkoxylation products 0.5-10 mg/tablet. The concentration ranges represent about 3 to about 35% of coated tablet weight for pseudoephedrine salt, about 10 to about 65% for acetaminophen and about 0.05 to about 1.5% for loratadine.

The hydrophilic polymers are present at a concentration of about 5 to about 15%, fillers at about 10 to about 20%, antiadherents at 0 to about 5%, lubricants at 0.25 to about 5%, and binders at 0 to about 3%, all percentages being relative to the tablet core weight.

The tablet coating comprises the loratadine or its decarbalkoxylation product, a hydrophilic polymer and a plasticizer as described above, i.e. a preferred polymer is HPMC USP 2910 and a preferred plasticizer is PEG, present in a preferred ratio of 5:1.

The following example is directed to a loratadine, acetaminophen and pseudoephedrine sulfate combination dosage form.

EXAMPLE 3	
A. Core Tablet	
	mg/tablet
Pseudoephedrine Sulfate	60
Acetaminophen 90%*	555
Dicalcium phosphate dihydrate	98
HPMC E4M	48
Stearic Acid	10
Magnesium Stearate	4
	775
* Equivalent to 500 mg acetaminophen	
B. Active Coating	
Loratadine	2.5
HPMC/PEG	5.0

Method of Manufacture

A. Core

1. Blend pseudoephedrine sulfate, acetaminophen, dicalcium phosphate dihydrate and HPMC E4M for 5-30 minutes in a suitable mixer.
2. Granulate the powder mix with a hydroalcoholic mixture.
3. Dry and mill the granulation using suitable size screen.
4. Compress into suitable size tablets.

B. Active Loratadine Coating

1. Dissolve HPMC/PEG in suitable amount of water or a water/alcohol mixture.
2. Disperse loratadine in the HPMC/PEG solution.
3. Coat tablets with the dispersion and polish the coated tablets using standard procedures.

While the invention has been described and illustrated with reference to certain preferred embodiments

thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit of the invention. For example, effective dosages of the active ingredients other than the preferred ranges set forth hereinabove may be used based on such factors as the age, weight and condition of the patient. It is intended that the invention be limited only by the scope of the claims which follow.

Claims

1. A sustained release pharmaceutical composition comprising a coated tablet wherein the tablet coating comprises an antihistaminic-effective amount of loratadine or 6-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and a hydrophilic polymer and the tablet core comprises an analgesic-effective amount of ibuprofen, a decongestant-effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and a swellable hydrophilic polymer, and wherein the tablet coating and the tablet core further comprise pharmaceutically acceptable excipients.
2. A composition of claim 1 wherein the tablet core comprises ibuprofen at about 10 to about 55% of the coated tablet weight, pseudoephedrine or a pharmaceutically acceptable salt thereof at about 3 to about 25% of the coated tablet weight, and a hydrophilic polymer at about 5 to about 15% of the tablet core weight.
3. A composition of claim 2 wherein the tablet core further comprises about 10 to about 20% filler, 0 to about 5% antiadherent, about 0.25 to about 5% lubricant and about 0.5 to about 3% binder.
4. A composition of claim 3 wherein the hydrophilic polymer is a cellulosic ether selected from the group consisting of methylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, carboxymethylcellulose, carboxyethylcellulose and mixtures thereof, and the filler is dibasic calcium phosphate or the dihydrate thereof, microcrystalline cellulose or lactose; the antiadherent is silicon dioxide or talc; the lubricant is magnesium stearate or stearic acid; and the binder is povidone or cornstarch.
5. A composition of claim 3 wherein the hydrophilic polymer is hydroxypropylmethylcellulose USP 2910 or is hydroxypropylmethylcellulose USP 2208 having a viscosity of 100,000 cps in a 2% aqueous solution; the filler is microcrystalline cellulose; the lubricant is magnesium stearate; and the binder is povidone.
6. A composition of claim 1 wherein the tablet core comprises 120 mg pseudoephedrine sulfate, 555 mg ibuprofen 90%, 100 mg hydroxypropylmethylcellulose USP 2208 having a viscosity of 100,000 cps in a 2% aqueous solution, 10 mg povidone, 154 mg microcrystalline cellulose and 5 mg magnesium stearate, and wherein the tablet coating comprises 5 mg loratadine and 10 mg of a 5:1 mixture of hydroxypropylmethylcellulose USP 2910 having a viscosity of 6 cps in a 2% aqueous solution and polyethylene glycol having a molecular weight of 300-6000.
7. A composition of claim 1 wherein the tablet core comprises 120 mg pseudoephedrine sulfate, 555 mg ibuprofen 90%, 150 mg hydroxypropylmethylcellulose USP 2910 having a viscosity of 4000 cps in a 2% aqueous solution, 75 mg povidone, 148.5 mg microcrystalline cellulose, 14 mg silicon dioxide and 5 mg magnesium stearate, and wherein the tablet coating comprises 5 mg loratadine and 10 mg of a 5:1 mixture of hydroxypropylmethylcellulose USP 2910 having a viscosity of 6 cps in a 2% aqueous solution and polyethylene glycol having a molecular weight of 300-6000.
8. A method of treating cold, cold-like and flu symptoms comprising administering a composition of claim 1 to a mammal in need of such treatment.
9. A sustained release pharmaceutical composition comprising a coated tablet wherein the tablet coating comprises an antihistaminic-effective amount of loratadine or 6-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and a hydrophilic polymer and the tablet core comprises an analgesic-effective amount of acetaminophen, a decongestant-effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and a swellable hydrophilic polymer, and wherein the tablet coating and the tablet core further comprise pharmaceutically acceptable excipients.
10. A composition of claim 13 wherein the tablet core comprises acetaminophen at about 10 to about 65% of the coated tablet weight, pseudoephedrine or a pharmaceutically acceptable salt thereof at about 3 to about 35% of the coated tablet weight, and a hydrophilic polymer at about 5 to about 15% of the tablet core weight.
11. A composition of claim 14 wherein the tablet core further comprises about 10 to about 20% filler, 0 to about 5% antiadherent, about 0.25 to about 5% lubricant and 0 to about 3% binder.
12. A composition of claim 14 wherein the hydrophilic polymer is a cellulosic ether selected from the group consisting of methylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, carboxymethylcellulose, carboxyethylcellulose and mixtures thereof, and the filler is dibasic calcium

phosphate or the dihydrate thereof, microcrystalline cellulose or lactose and the lubricant is magnesium stearate or stearic acid.

13. A composition of claim 15 wherein the hydrophilic polymer is hydroxypropylmethylcellulose USP 2910 or is hydroxypropylmethylcellulose USP 2208 having a viscosity of 100.000 cps in a 2% aqueous solution; the filler is dibasic calcium phosphate dihydrate; and the lubricant is magnesium stearate and stearic acid.

14. A composition of claim 13 wherein the tablet core comprises 60 mg pseudoephedrine sulfate, 555 mg acetaminophen 90%, 48 mg hydroxypropylmethylcellulose USP 2910 having a viscosity of 4000 cps in a 2% aqueous solution, 98 dibasic calcium phosphate dihydrate, 10 mg stearic acid and 4 mg magnesium stearate, and wherein the tablet coating comprises 2.5 mg loratadine and 5 mg of a 5:1 mixture of hydroxypropylmethylcellulose USP 2910 having a viscosity of 6 cps in a 2% aqueous solution and polyethylene glycol having a molecular weight of 300-6000.

15. A method of treating cold, cold-like and flu symptoms comprising administering a composition of claim 13 to a mammal in need of such treatment.

15

20

25

30

35

40

45

50

55



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

Application number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 90304792.6
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D, A	<u>US - A - 4 783 465</u> (A. SUNSHINE et al.) * Abstract; claims 1,2,24; column 11, line 61 - column 12, line 20; column 12, line 51 - column 13, line 21 *	1-7	A 61 K 31/445 A 61 K 31/19 A 61 K 31/135 A 61 K 9/24
D, A	<u>US - A - 4 659 716</u> (F.J. VILLANI, J.K. WONG) * Claims 5-10; examples V,VIB; column 6, line 62 - column 8, line 46; especially column 8, lines 44-46 *	1-7, 9-14	
D, A	<u>US - A - 4 282 233</u> (F. J. VILANI) * Claim 12; example 1B; column 4, line 42 - column 5, line 42 *	1-7, 9- 14	
D, A	<u>US - A - 4 619 934</u> (A. SUNSHINE et al.) * Abstract; claims 1-3; columns 4,5, line 25 *	1-7	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K 31/00 A 61 K 9/00
INCOMPLETE SEARCH The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims. Claims searched completely: 1-7, 9-14 Claims searched incompletely: - Claims not searched: 8, 15 (method for treatment of the human Reason for the limitation of the search: or animal body by therapy - EPC Article 52 (4))			
Place of search VIENNA		Date of completion of the search 03-07-1990	Examiner MAZZUCCO
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

EPO Form 1505.1.03&2

